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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,325	08/02/2003	David P. Summers	ENDO/514US	4206

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EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,325	SUMMERS ET AL.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 02 August 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HL

CLAIMS 1-11 ARE PRESENTED FOR EXAMINATION

Specification

The disclosure is objected to because of the following informality:

At page 1, line 3 "60/60/400,649" should read as ---60/400,649.

Appropriate correction is required.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mobilizing muscle cells, including endogenous muscle stem cells, to a specific muscle mass, does not reasonably provide enablement for doing the same with exogenous stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

It should be noted that the Korbling et al. reference relied on below was published August 7, 2003, which is subsequent to Applicants' earliest priority date of August 2, 2002. However, it is proper for the Examiner to rely on this reference because it establishes the state of the art concerning the use of exogenous stem cells at or around the date of Applicants' invention. "In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of

what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) because it establishes the state of the art at or around the date of Applicants' invention.", (see MPEP § 2164.05(a)).

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the appropriate factors from those above are applied to the present application (see below) and weighed, it is the examiner's position that the present specification would not enable one skilled in the art to develop muscle mass in a mammal by stimulating, recruiting and mobilizing muscle cells to a specific muscle mass where the muscle cells are differentiated from exogenous stem cells.

(1) The nature of the invention/breadth of the claims.

The claims are directed to methods for developing muscle mass in a mammal by stimulating, recruiting and mobilizing muscle cells to a specific muscle mass, the method comprising administering nicotine or nicotine acetylcholine receptor agonist (nAChR) to a

mammal in an amount sufficient combined with exercise to increase muscle mass. Claim 2 indicates that the muscles cells are differentiated from stem cells and claim 4 indicates that the stem cells are exogenous, i.e., stem cells not present in the mammal.

(2) The amount of direction or guidance presented and presence or absence of working examples.

The specification provides merely provides the statements above in (1) that exogenous stem cells may be used. The specification is devoid of any specific means by which such stem cells are collected, prepared or administered. No experimental data is present that shows muscle mass may be developed by using exogenous stem cells.

(3) State of the Art/The quantity of experimentation necessary.

The state of the art is such that the use of exogenous stem cells for therapeutic purposes is underdeveloped and that their use in therapeutic applications would be unpredictable. In support of this, Korbling et al. (cited by the Examiner on the attached form PTO-892, reference "U") teaches:

"Assuming that circulating stem cells generate cells specific to solid organs in vivo, a *potential* clinical *concept* of tissue repair would require three conditions. First, the stem-cell pool must be easily accessible, as is the case with the circulating stem-cell pool that is routinely used for harvesting hematopoietic stem cells. Second, the concentration of stem cells at the site of tissue regeneration must be sufficient, which can be accomplished either by cytokine-induced mobilization of hematopoietic stem cells, mesenchymal stem cells, angioblasts, and smooth-muscle progenitor cells from extravascular sites into the circulating blood or by directly delivering the cells to the site of tissue injury. Third, appropriate signals from the site of damaged tissue *must direct exogenous stem cells* to the site where they are needed. *However, we do not yet clearly understand how to manipulate the microenvironment surrounding the are of tissue regeneration actively and signal exogenous blood-derived stem cells to participate in*

tissue regeneration in vivo.(emphasis added)(section bridging pages 6-7).

Further, as taught by Caterson et al. (cited by the Examiner, reference "V" on the attached, form PTO-892):

"Mesenchymal stem cells are a rare population of undifferentiated cells, isolated from adult tissue sources, that have the capacity to differentiate into mesodermal lineages, including bone, fat, muscle, cartilage, tendon, and marrow stroma." (page 1, line 1 of the abstract). "The ultimate goal is directed cellular regeneration of damaged or diseased musculoskeletal tissue. *Currently, the limitation is our knowledge and ability to direct this differentiation*, but with further study molecular orthopaedic interventions should become a reality." (emphasis added)(page 1, last lines of the abstract).

Applicants have failed to provide guidance and information sufficient to allow the skilled artisan to ascertain how to direct exogenous stem cells to produce muscle cells and then to direct such cells to the area of need in the mammal. From the state of the art as discussed above, the artisan would be unaware of how to accomplish this objective. Accordingly, undue experimentation would be involved.

Claims 2+3 Enabled

It is believed that claims 2 and 3 are enabled because such would be inherently accomplished in the body of a mammal in which the claimed method is practiced. Claim 2 requires that the muscle cells are differentiated from stem cells and claim 3 requires that the stem cells be endogenous. At page 2 of the specification, lines 6-7, it is set forth that "It would seem that a process that enables the body to add or subtract various tissues through the use of the endogenous regulation of cells would be a major benefit to society. Accordingly, it is deemed

that the combination of claim 2 plus claim 3 is interpreted to mean that by administering the active agents of claim 1 and exercising, Applicants are facilitating the body's own natural response to muscle "injury". In support of this, the article by Hawke (cited by the Examiner as reference "X" on the attached form PTO-892) is relied on to show that the body has resident stem cell populations on skeletal muscle fibers (see page 1 at the Abstract). Also, it is taught that these stem cells, a.k.a. myogenic progenitor cells (MPCs), "are quiescent in the unstressed muscle, but can reenter the cell cycle (become activated) in response to signals associated with muscle damage. After activation, these cells will proliferate and migrate to the site of injury to repair or replace damaged myofibers by fusing together and/or fusing to existing myofibers." (page 1 under the heading "Resident Muscle Stem Cell Poplulations"). Insofar as the "injury" referred to in the article may be interpreted as injury due to stressing the muscle through excercise, it is believed that the skilled artisan could practice the invention of claim 2 PLUS claim 3.

Summary

As the cited art and discussion above establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that muscle mass could be developed through the presumed administration of exogenous muscle stem cells. In order to actually achieve this aspect of the invention, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize and Applicant has failed to demonstrate how exogenous stem cells could be used to accomplish muscle mass development, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to

practice this embodiment of the claimed invention. This is so because the skilled artisan would view this objective as unpredictable based on knowledge in the art. Accordingly, claims 1, 2, 4-11 are deemed properly rejected.

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, line 4, "muscle mass" appears to be directed to the "specific muscle mass" at line 2. The antecedent basis for this term is unclear. It is recommended that at line 4, "muscle mass" be amended to read "said specific muscle mass" in order to overcome this point of rejection.

In claims 5, 6, 8, 9 and 10, the expressions "the muscle mass" (claims 5 and 6), "the target physiological tissue or muscle mass" (claim 8), "muscle mass or physiologic tissue" (claim 9), and "tissue mass" (claim 10) have no clear antecedent basis. In order to overcome this point of rejection, it is suggested that the references to muscle mass be made specific to the "specific muscle mass" at line 2 of claim 1. Also, in order to avoid an issue under 35 U.S.C. 112, first paragraph, the expressions "physiological tissue" and "tissue mass" be deleted because the present invention is clearly directed to increasing muscle mass and not tissue mass in general.

Respecting claim 5, it is pointed out that "The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is

informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention." (MPEP 2173).

The expression "a normal life style" in claim 5 is a relative term which renders the claim indefinite. The expression "normal life style" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and thus one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Because the expression "normal life style" has not been defined, it would require subjective interpretations of whether or not a particular life style is included by or excluded from the present claims. It is therefore the Examiner's position that the public would not be informed of the boundaries of what constitutes infringement of the present claims and thus the claims fail to meet either the tenor or express requirements of 35 U.S.C. § 112, second paragraph and are properly rejected.

Cooke et al. (U.S. Patent No. 6,720,340)

Cooke et al. appears to be the closest prior art to the presently claimed subject matter. Cooke et al. are directed to the administration of nicotine receptor agonists, such as nicotine, for recruiting bone marrow-derived stem cells in the treatment of conditions amenable to such recruitment, e.g., neutropenia (see the abstract). The cells that may be recruited include "mesenchymal progenitor cells", including endothelial progenitor cells and other cells dedicated to development into cells of mesenchymal lineages, e.g., connective tissue, cartilage,

chondrocytes, bone (osteoblasts), fat cells (adipocytes), and the outer layers of blood vessels (see col. 6, lines 62-67). The conditions that may be treated include "any condition associated with an obstruction of a blood vessel, e.g., obstruction of an artery, vein, or of a capillary system. Specific examples of such conditions or disease include, but are not necessarily limited to, coronary occlusive disease, carotid occlusive disease, arterial occlusive disease, peripheral arterial disease, atherosclerosis, myointimal hyperplasia (e.g., due to vascular surgery or balloon angioplasty or vascular stenting), thromboangiutis obliterans, thrombotic disorders, vasculitis, and the like." (see col. 14, lines 37-47). Other types of immune-associated disorders are disclosed at col. 16, lines 6-21.

However, the disclosure of Cooke et al. is lacking the necessary information to bring to one of ordinary skill in the art the concept that muscle mass may be developed through the administration of nicotine receptor agonists, such as nicotine, and in combination with excercise, which involves stimulating, recruiting and mobilizing muscle cells that are differentiated from endogenous stem cells.

Accordingly, the present claims have not been rejected over the disclosure of Cooke et al.

The references cited on the attached from PTO-892 and not relied on by the Examiner are included to show the general state of the art.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Raymond J Henley III
Primary Examiner
Art Unit 1614

July 15, 2005